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Please I need,

RAVANAT (C.), FREUND (M.), MOOG (S.), MANGIN (P.), AZORSA (D.), SCHWARTZ (C.), LANZA (F.), CAZENAVE (J.-P.)

Differential effects of monoclonal antibodies to rat GPIIb-IIIa, GPIba or GPV on platelet function and in vivo survival.

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Differential Effects of Monoclonal Antibodies to Rat GPIIb-IIIa, GPIb or GPV on Platelet Function and In Vivo Survival

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MoAbs to platelet GPIIb-IIIa are powerful inhibitors of platelet aggregation and are used clinically as antithrombotic drugs, where the main complications are thrombocytopenia and bleeding. In our laboratory, we have produced MoAbs to the rat aggregation receptor (GPIIb-IIIa (RPM1 and 10) and to GPIb (RM14 and 15) and GPV (RPM4 and 9), subunits of the GPIb-V-IX adhesion complex. Specificity was demonstrated by immunoprecipitation of the proteins from biotinylated platelets and all MoAbs recognized resting platelets and megakaryocytes by immunocytochemistry and FACS. FACS showed that RPM4 and 9 recognized intact platelet GPV but not platelets exposed to thrombin or elastase. RPM14 and 15 similarly recognized intact platelet GPIb but not platelets treated with elastase. The MoAbs were then tested in studies of *in vitro* platelet function and *in vivo* platelet recovery and survival in rats. RPM15 inhibited the binding of von Willebrand factor to platelets, while the anti-GPIIb-IIIa MoAbs bolus injection (1 mg/kg iv), all MoAbs induced a drop in circulating platelets as compared to rats receiving saline or irrelevant MoAbs, with a variable degree of thrombocytopenia depending on the class of MoAb. One day after injection of anti-GPV the platelet count had progressively decreased by 50 to 80% and normal levels ($9x10^5$ platelets/µl) were restored 2 to 3 days later. In contrast, after injection of anti-GPIIb-IIIa, most platelets (95%) were immediately removed from the circulation. Recovery started as soon as 1 h later and reached normal levels after 3 days. Injection of anti-GPIb also led to a rapid drop in platelets (95%), but only 20% had recovered after 1 day and thrombocytopenia remained steady for the next 10 days ($2x10^5$ platelets/µl). Platelet survival was assessed by pretreating rats with MoAbs before injection of ^{111}In labeled platelets. In animals treated with anti-GPIb or anti-GPIIb-IIIa, platelets were transiently sequestrated in the spleen but circulated again with normal survival (3 to 4 days). Conversely, treatment with anti-GPV reduced platelet survival to 2 h (RPM4) or 2 days (RPM9). Thus MoAbs to GPIIb-IIIa or GPIb induced thrombocytopenia by mechanisms different to those of non-blocking anti-GPV MoAbs. This could be relevant to the thrombocytopenia encountered during treatment with platelet GPIIb-IIIa inhibitors or to immune thrombocytopenia. In conclusion, the study of MoAbs to different platelet membrane glycoprotein epitopes in a rat system might prove useful to elucidate the mechanisms of platelet function and *in vivo* survival.